Armed Forces College of Medicine

AFCM

Applied Biochemistry (2)

Neuroscience Module

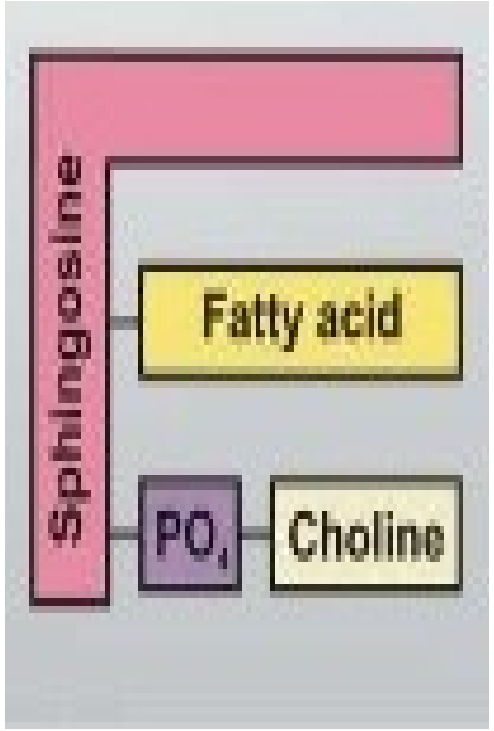
INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

1- Describe the metabolic pathways supplying CNS with metabolic fuels in the fasting state

2- Correlate vitamins A, B1, B12 and folic acid deficiencies to their clinical disorders

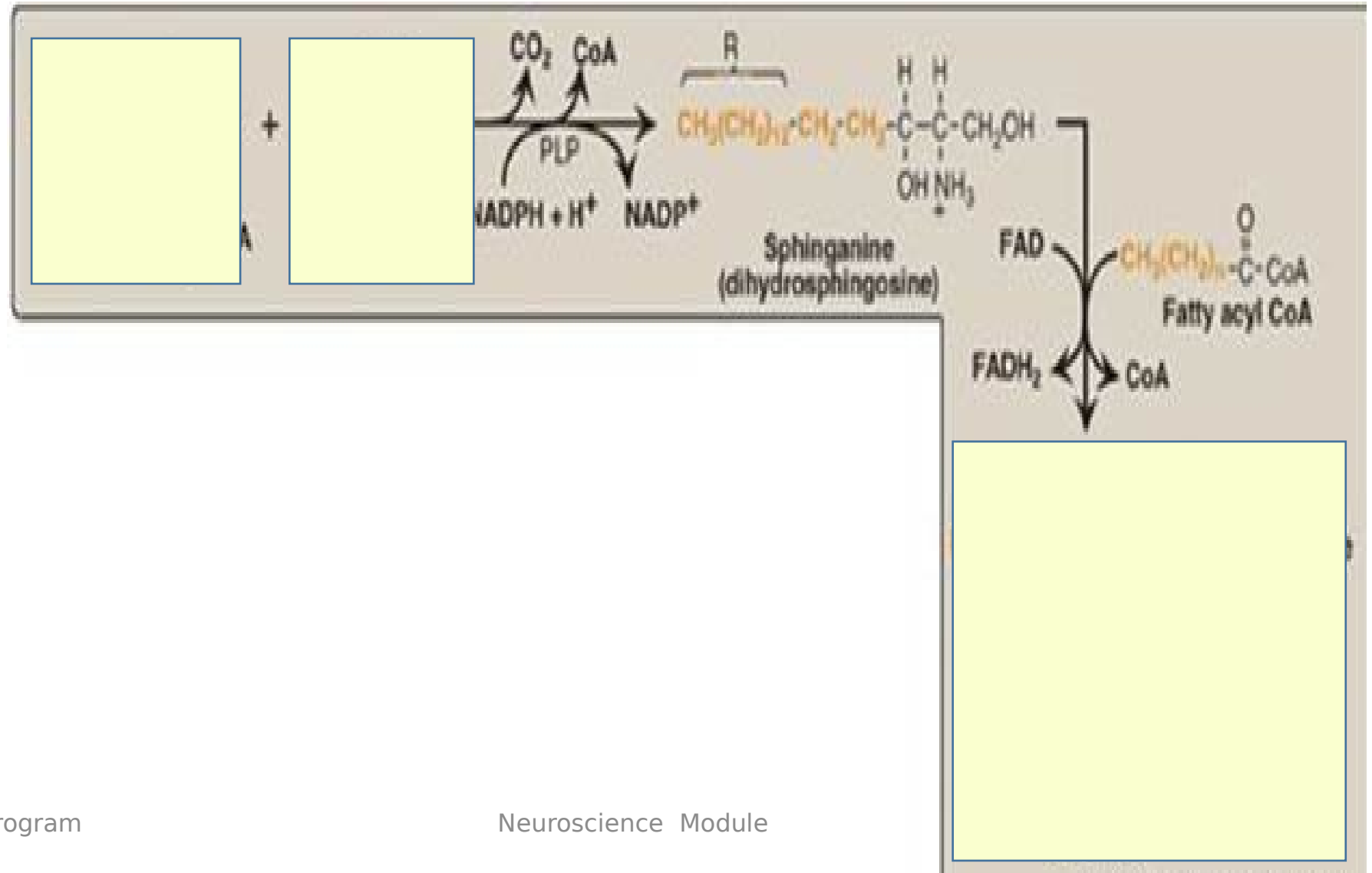
Identify the following and mention one importance.

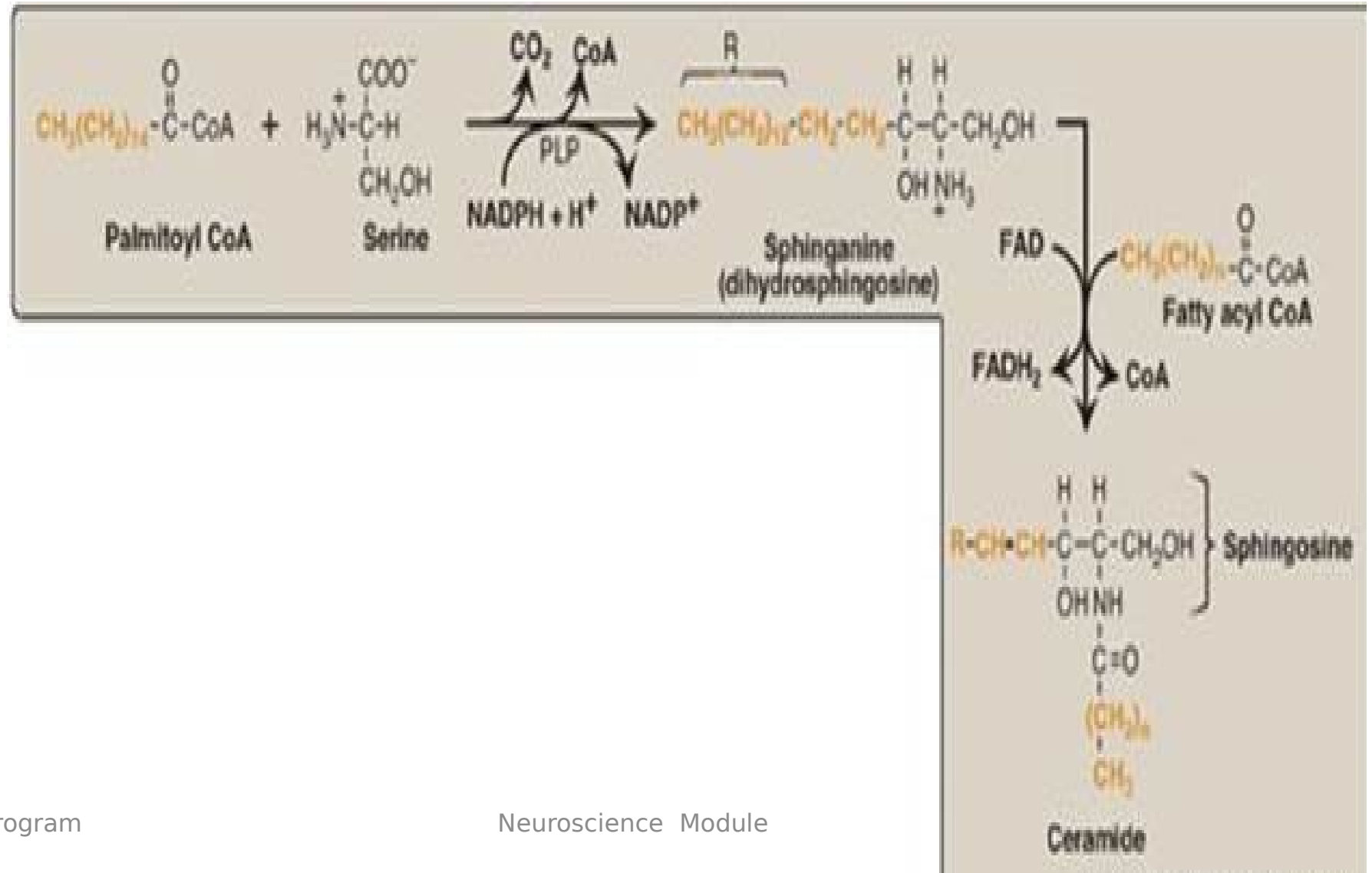


Sphingomyelin
= Ceramide + Phosphocholine

Sphingomyelin is a major structural lipid in the membranes of nerve tissue.

Identify the missing.

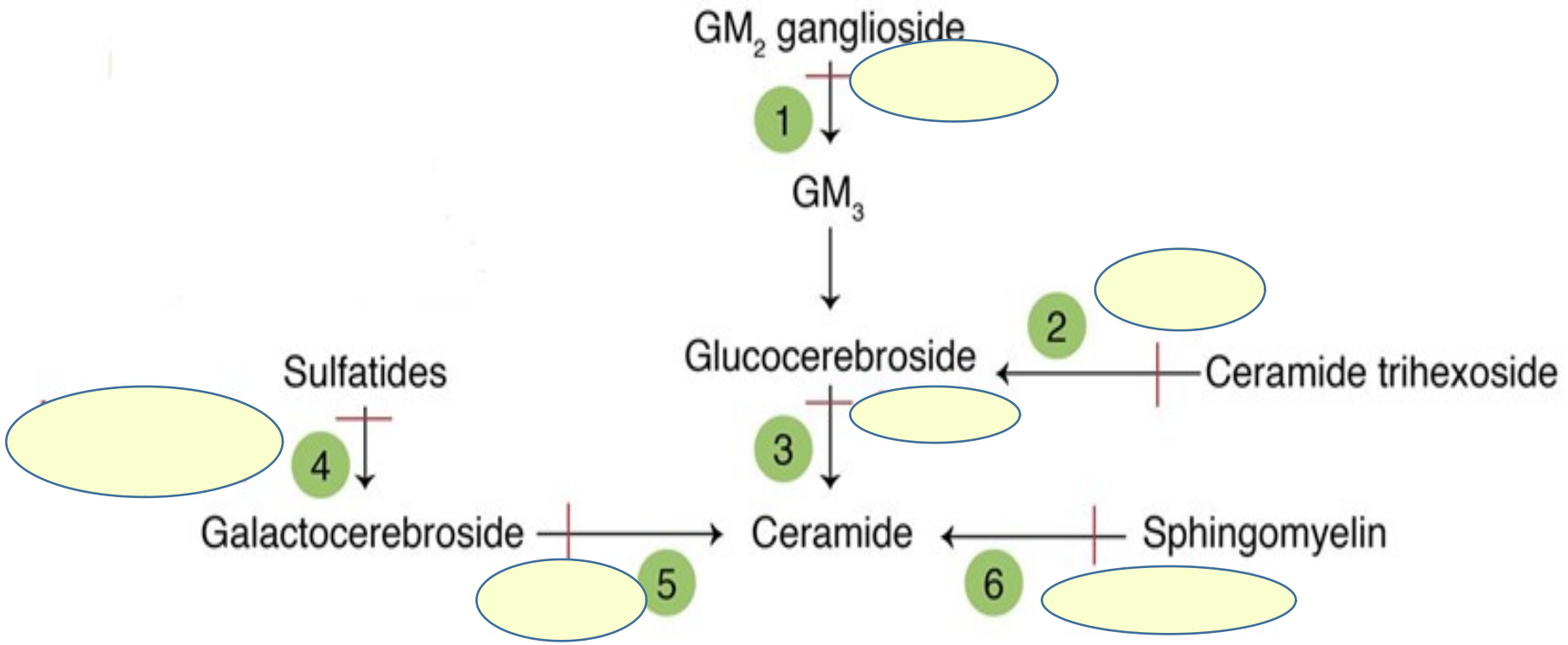



Palmitoyl CoA
Serine
CO2
CoA
PLP
NADPH + H+
NADP+
R
Sphinganine
(dihydrosphingosine)
FAD
FADH2
CoA
Fatty acyl CoA
Sphingosine
Ceramide

Complete the missing as regarding sphingolipidoses

Tay-Sachs disease		Ganglioside	Rapidly progressing &
Niemann-Pick	Sphingomyelinase		Mental retardation l e)
	Glucocerebrosidase	des	mental retardation in infantile form only

If the numbered steps are defective, different types of sphingolipidoses may result. Name the enzyme of each step and the disease that may result from its deficiency.



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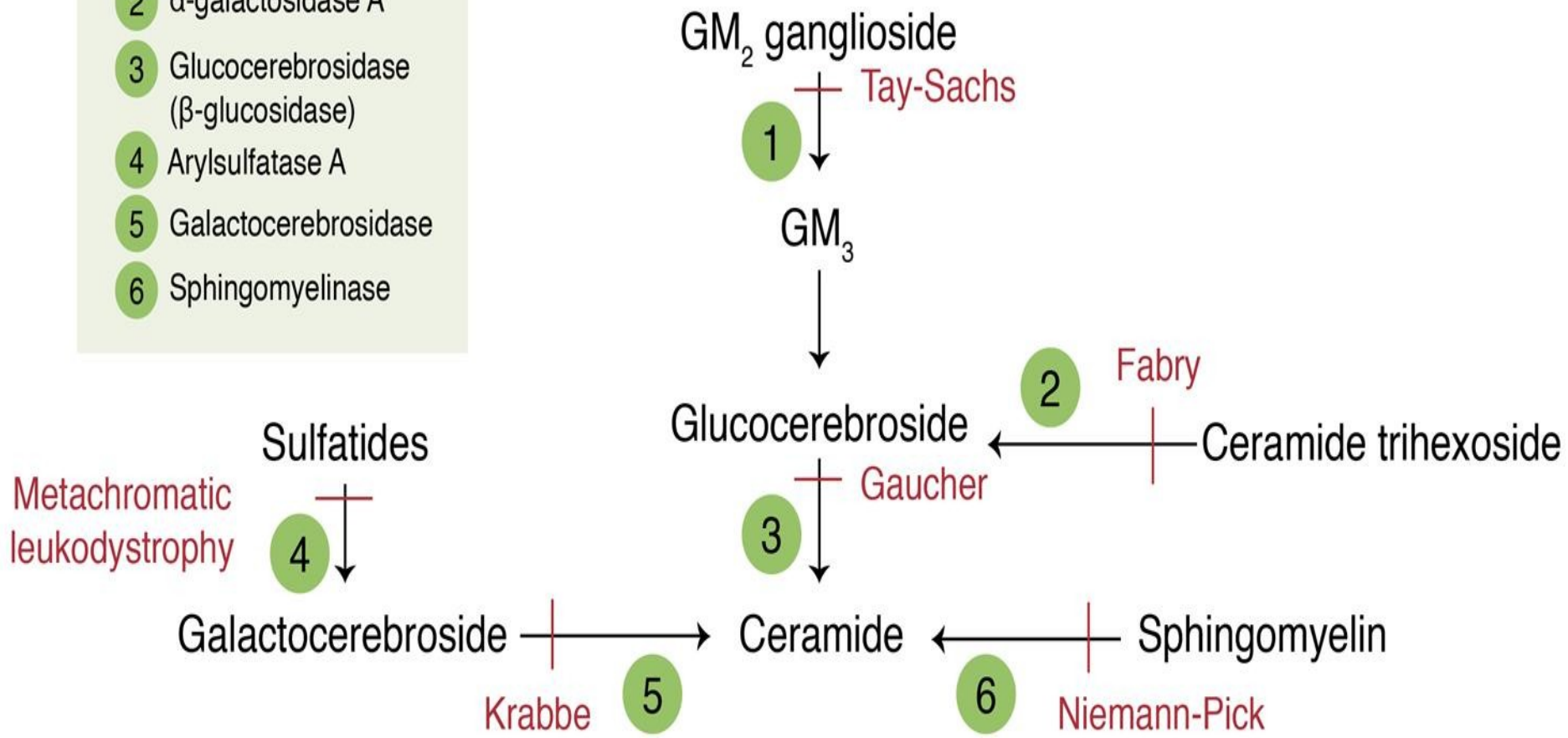
Lysosomal Storage Disorders

1. Hexosaminidase A
2. α-galactosidase A
3. Glucocerebrosidase (β-glucosidase)
4. Arylsulfatase A
5. Galactocerebrosidase
6. Sphingomyelinase



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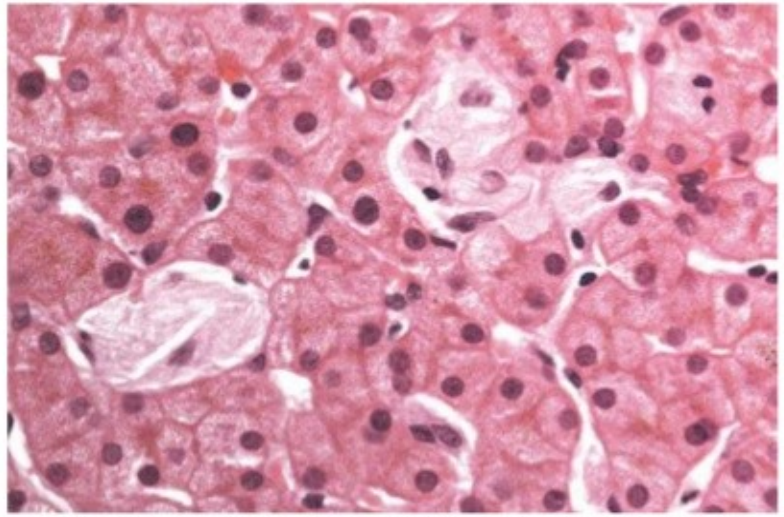
Lucy Liu

Case presentation

A 2-year old boy presents with hepatosplenomegaly, pallor, bruising and delayed mental development. A liver biopsy shows wrinkled looking cells. He was diagnosed as Gaucher's disease.

Gaucher's disease



Pale-staining, striated Kupffer cells containing stored lipid are present within sinusoids. The affected cells compress hepatocytes and sinusoids and may give rise to portal hypertension. Pericellular fibrosis is a common finding

Which enzyme may be affected in the enzyme assay?

The wrinkled looking cells indicate accumulation of which substrate?

What is the main line of treatment?

Which enzyme may be affected in the enzyme assay?

β–Glucocerebrosidase

The wrinkled looking cells indicate accumulation of which substrate?

Glucocerebrosides

What is the main line of treatment?

Enzyme replacement therapy

Case presentation

A 15-month-old female infant is brought to the emergency room by her parents. The mother does reveal that the infant 'doesn't seem like her other children and with developmental delay."' Physical examination reveals a distressed infant who does not verbalize. Her abdomen is tender and enlargement of both spleen and liver are present. After a brief hospital course, the infant dies and autopsy is performed. Neural tissue shows electrondense material within lysosomes and Niemann Pick disease was diagnosed. A defect in which of the following was most likely present in this infant?

a) Degradation of ganglioside GM2
b) Degradation of glucocerebrosides
c) Degradation of sphingomyelin
d) Synthesis of gangliosides

Case scenario

A 35-year-old female became severely depressed after the sudden death of her husband. Two months later, she was brought to the emergency room

Case scenario

She appeared thin and pale. She had fruity odor of breath. Questioning revealed that she has not eaten for several days. Analysis of a blood sample revealed low blood glucose level (55 mg/dL) and elevated levels o

Name the three ketone bodies, and why are they important in metabolism?

Ketone Bodies (KB)

1. Acetoacetate

2. β-hydroxybutyrate

3. Acetone.

Why are KB important for peripheral tissues as a source of energy?

Because they are:

1) **Soluble** in water do not need lipoproteins or albumin as do the other lipids. Thus, they are ***transported across the inner mitochondrial membrane as well as across the blood-brain barrier and cell membranes***.

2) **Produced in the liver** when acetyl CoA

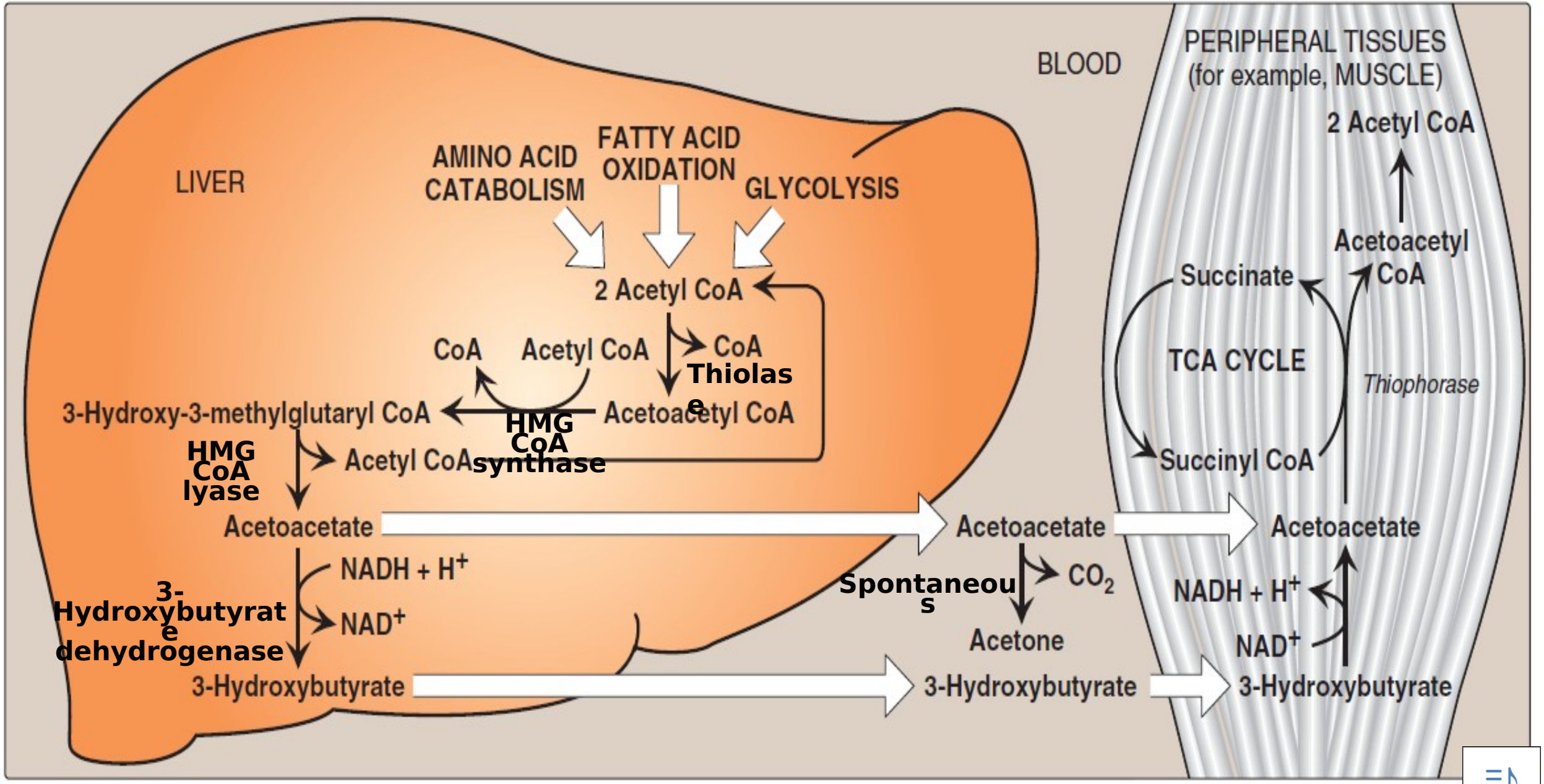
Why are KB important for peripheral tissues as a source of energy?

Because they are:

3) **Used by extrahepatic tissues (skeletal and cardiac muscles and renal cortex). Even the brain can use ketone bodies to help meet its energy needs if the blood levels rise sufficiently.**

4) **Important during prolonged periods of fasting, thus ketone bodies spare glucose.**

How are ketone bodies metabolized (enzymes, pathways, location)?



Ketogenesis (Liver) and Ketolysis

Define ketosis, and name conditions where it occurs.

Ketosis

Ketogenesis >Ketolysis

It is a metabolic disorder characterized by a triad of:

1. **Ketonemia (increase ketone bodies in blood).**
2. **Ketonuria (increase ketone bodies in urine).**
3. **Acetone (fruity) odor of breath.**

Normally ketone bodies:
in blood 0.5-3mg/dL
in urine <15mg/day

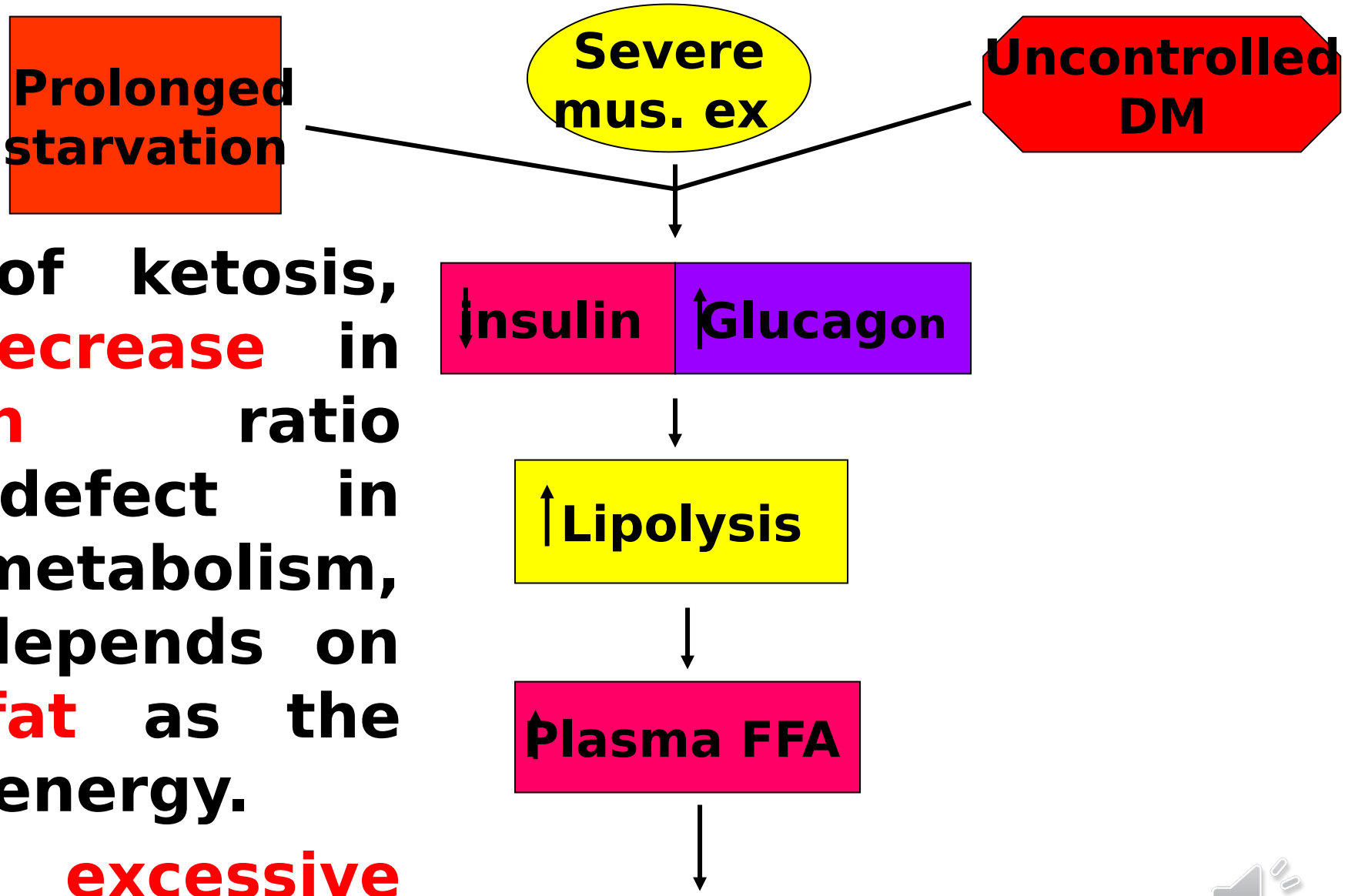
Ketosis

Causes of Ketosis:

1. Prolonged starvation.
2. low carbohydrates and high fat in diet
3. Uncontrolled diabetes mellitus type I.
4. Prolonged and severe muscular exercise
5. Prolonged administration of anti-insulin hormones.

Explain the mechanism of ketosis.

Mechanism of Ketosis:

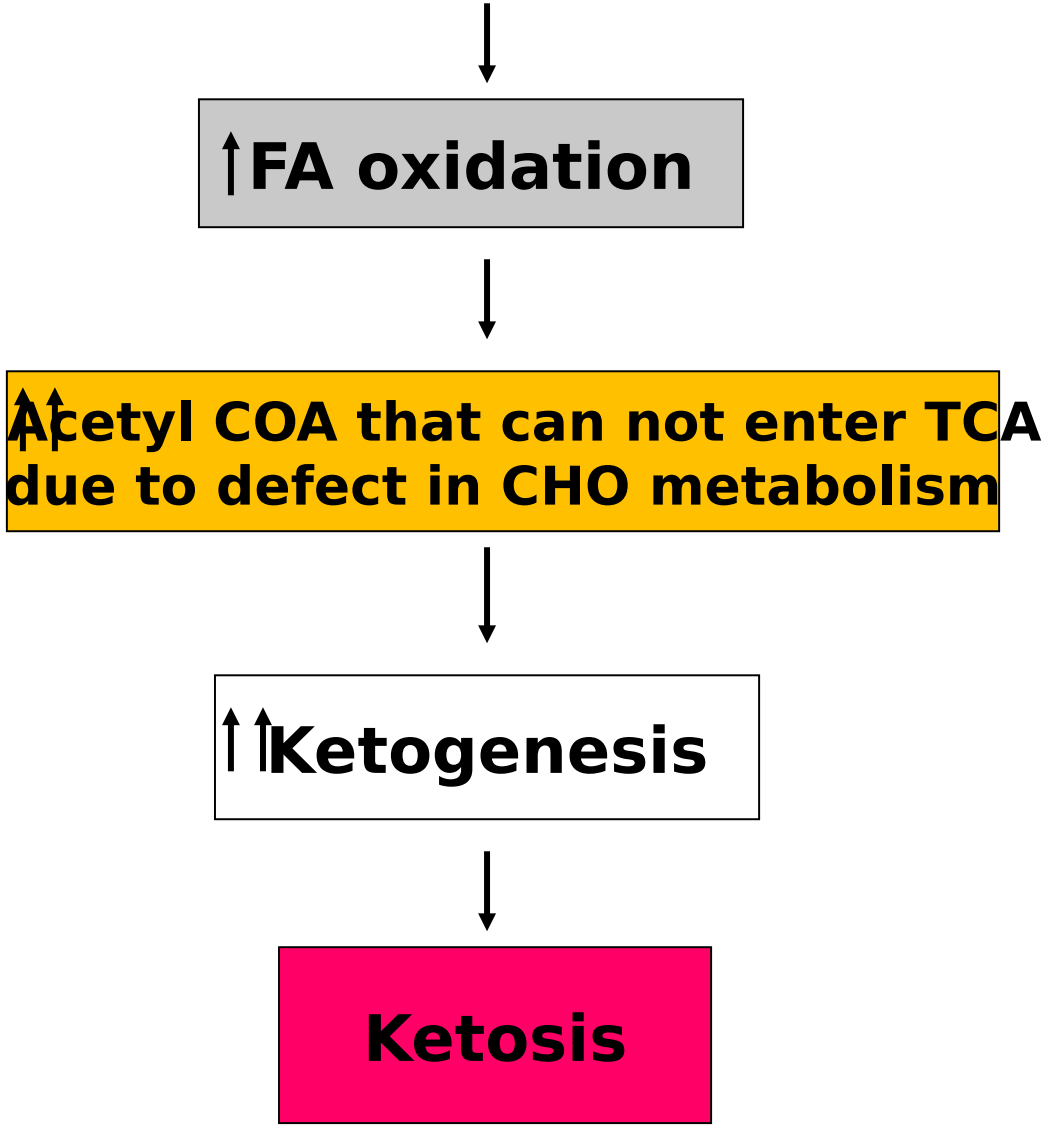


- In all types of ketosis, there is a **decrease** in **insulin/glucagon** ratio causing a defect in carbohydrate metabolism, so the body depends on **oxidation of fat** as the main source of energy.
- So, there is **excessive lipolysis** in adipose tissue

Mechanism of

Ketosis:

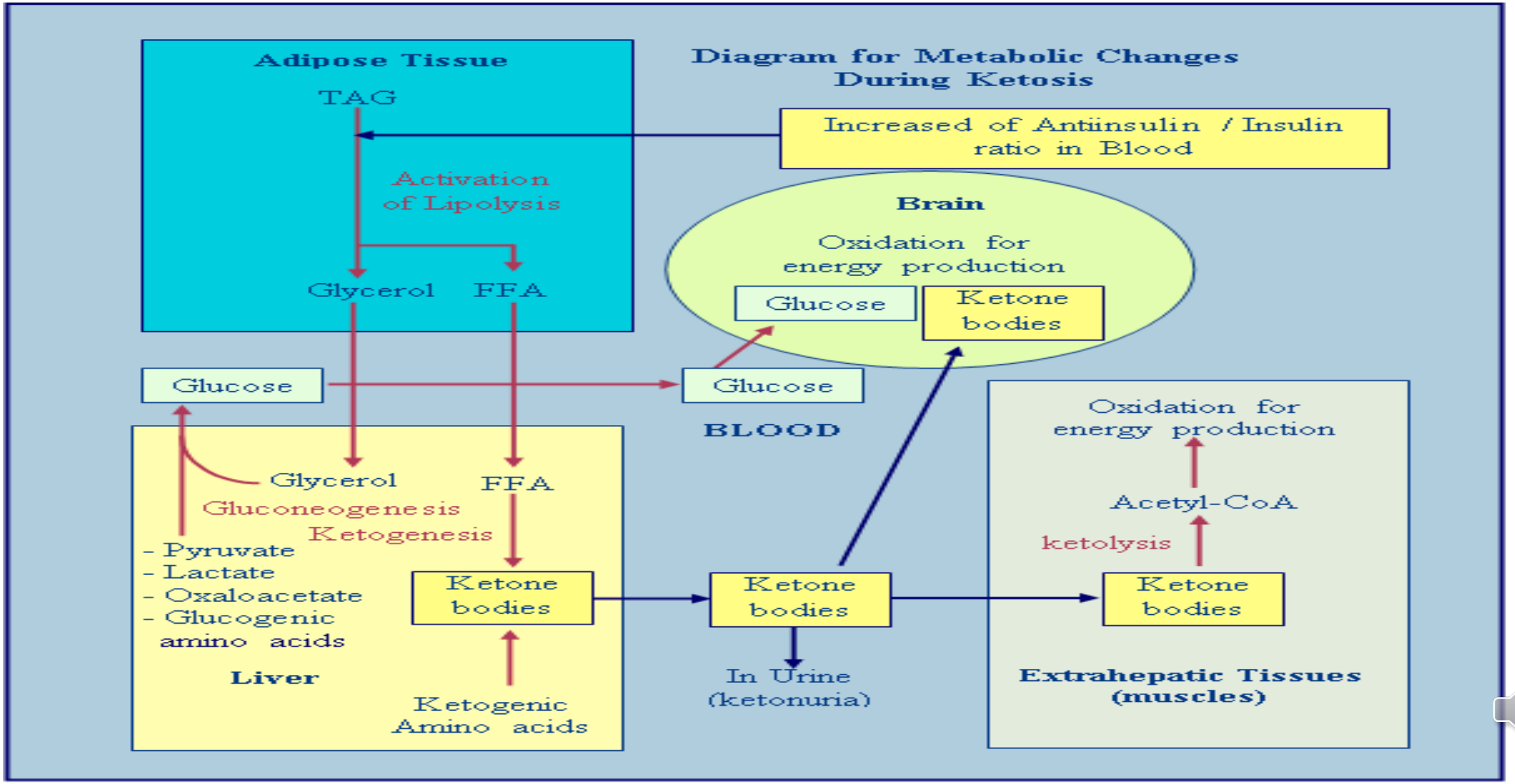
- The latter are oxidized to produce large amounts of acetyl COA that can not enter the citric acid cycle due to deficiency of oxaloacetate.
- Consequently, acetyl COA is diverted to the pathway of ketogenesis leading to excessive formation of



What are the metabolic changes during ketosis.

Metabolic Changes during ketosis

There is a decrease in the insulin/anti-



Compare between water- and fat-soluble vitamin

According to solubility, vitamins are classified into water-soluble and lipid-soluble vitamins

	Water-Soluble Vitamins	Lipid-Soluble Vitamins
	Vitamin C Vitamin B (8 members)	Vitamins A, D, K, and E
Intestinal absorption	Vitamin B12 needs a specific glycoprotein (intrinsic factor)	- Need bile acids - Affected by biliary obstruction
Transport in blood	May have specific transporter (e.g. transcobalamine for B12)	By lipoproteins and/or by Specific transport proteins
Urinary excretion	excreted once their concentration exceeds the renal threshold	Not excreted because insoluble in water
Storage in human body	No storage (Vitamin B12 is an exception)	Stored mainly in the liver
Toxicity due to excess intake	No toxicity	Toxicity occurs (Vitamin E is an exception)
Coenzyme function	Form coenzymes necessary for energy production or for hematopoiesis	Only vitamin K has coenzyme function

Case presentation

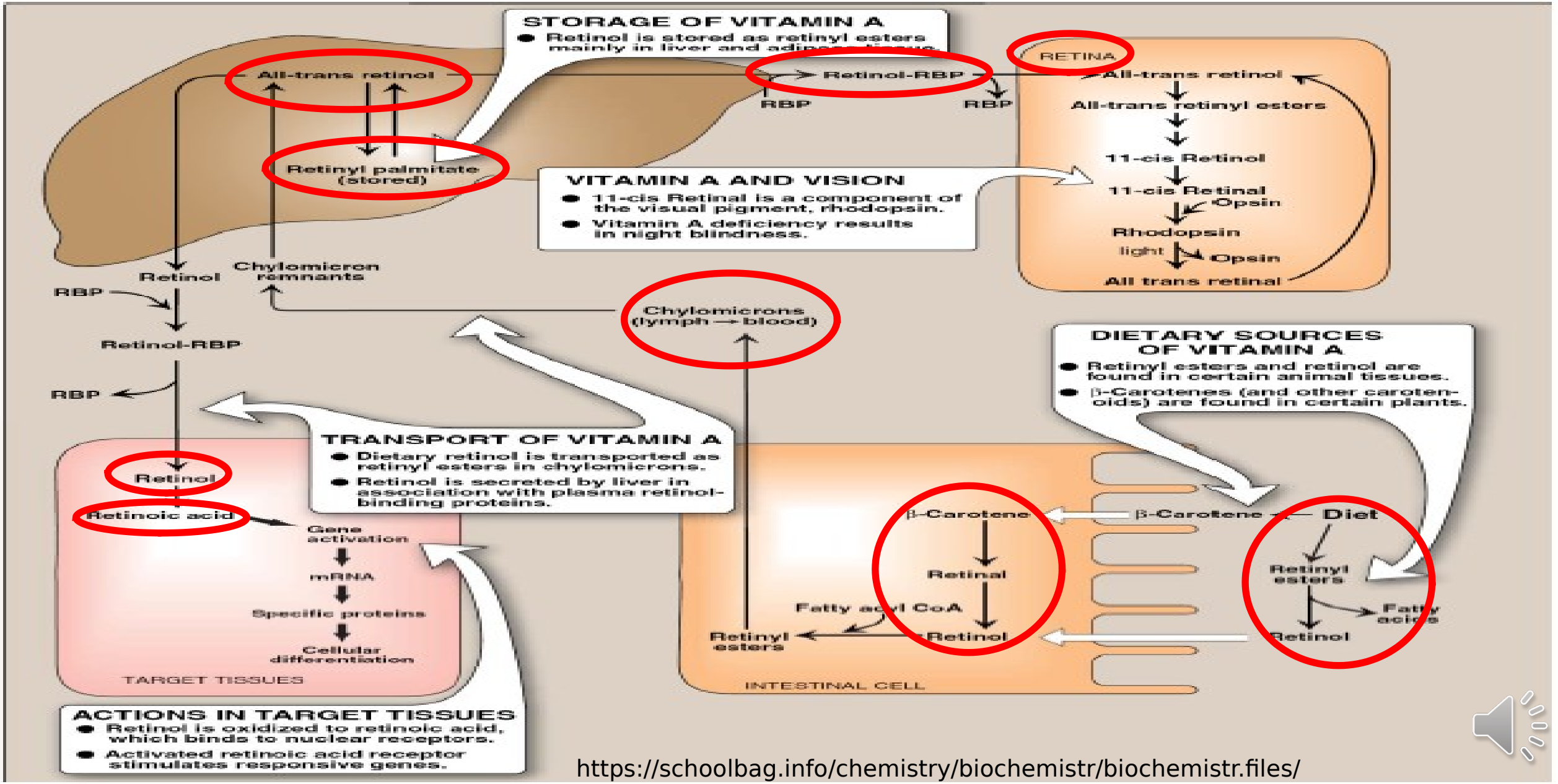
Nader was driving home one evening after dark and he realized he suffered from difficulty in seeing the markers on the road increasing gradually over past 6 months. His eyes were itchy and dry. He gave a history of malabsorption, intestinal bypass surgery and, more recently, bariatric surgery.

What is the possible diagnosis?

Vitamin A deficiency

Impairment in night vision due to decrease absorption

Absorption and transport of vitamin A



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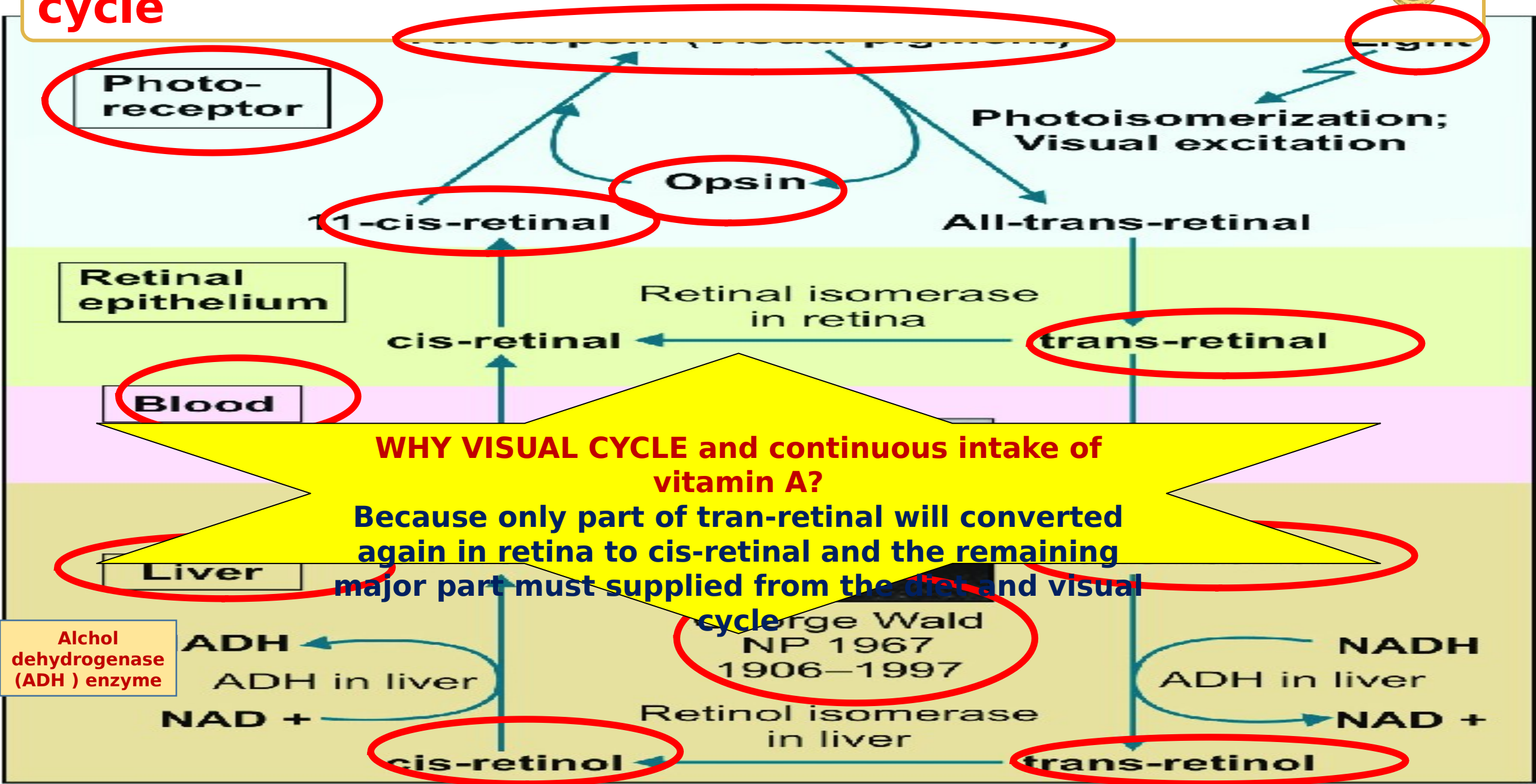
Role of Vitamin A in vision: visual cycle ; Wald's visual cycle



Which of the following is NOT a cause of vitamin A deficiency?

a)Decreased intake.

b)Obstructive jaundice

c)Hemolytic anemia

d)Cirrhosis of liver

e)Chronic nephrosis

Retinoids (Vitamin A) have the following functio

a) Retinal → normal vision.

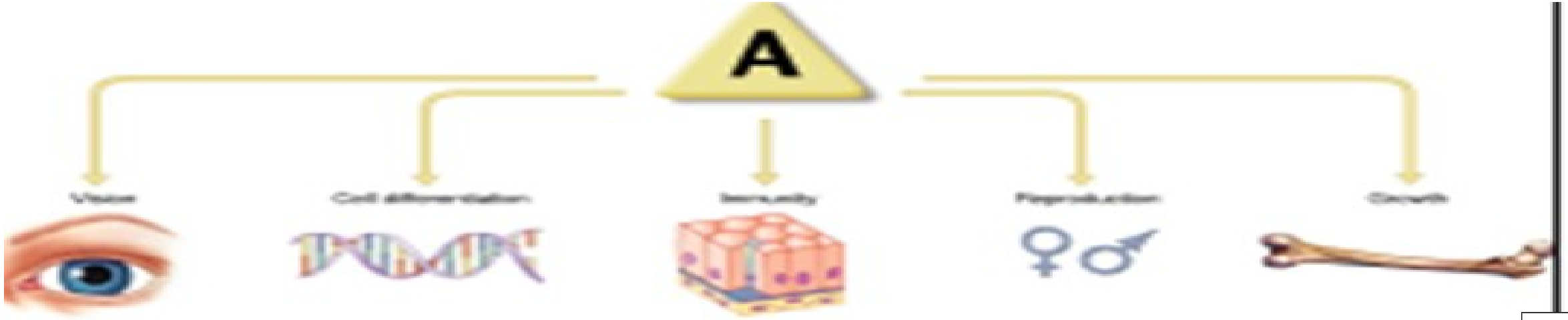
b) Retinol → normal reproduction .

c) Retinoic acid → normal growth & differentiation of epithelial tissue and mucus secretion → supports the body's barrier against infections &

→

defense against pathogens(if decrease → recurrent infections).

d) β-carotenes → antioxidants.



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Case presentation

Sarah is flight attendant. Her meals are often airplane vegetarian food when she wasn't tending to passengers. She encountered frequent fevers, and usually took antibiotics to shorten the duration required to cure so

can continue wit

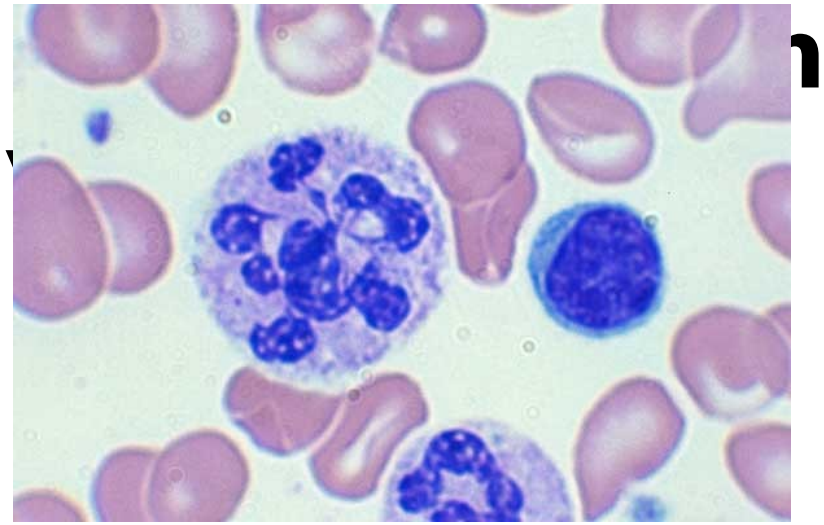
Case presentation

Lately she had been unable to concentrate. she had tingling sensation in her legs, and she had a headache. She could barely remember the country from which her latest flight had returned.

Case presentation

Sarah sought medical advice, she was checked physically and her blood pressure was found to be high, in spite she mainly ate low fat vegetables.

Her blood picture showed RBCs count to be $3x10^6$ /ml (normal count: ml), associated with abnormall



Enumerate causes of vitamin B12 deficiency

Causes :

- **Failure of absorption of B_{12}**
  - **Malabsorption diseases**
  - **Gastrectomy (Bypass operation & gastric sleeve)**
  - **Autoimmune destruction of the gastric parietal cells** (IF) → **pernicious anemia**
  - **Malfunctioning of gastric parietal cells e.g. in elderly subjects → decreased secretion of intrinsic factor→ B12 malabsorption.**
- **Dietary deficiency** among **vegetarians**.

Which of the following reactions require the presence of vitamin B12?

a)Conversion of acetyl CoA to citrate

b)Conversion of methylmalonyl coA to succinyl coA

c)Conversion of cysteine to methionine

d) A&B

e)B&C

Which of the following metabolites is likely to be increased in urine of patients with vitamin B12 deficiency?

a)Methionine

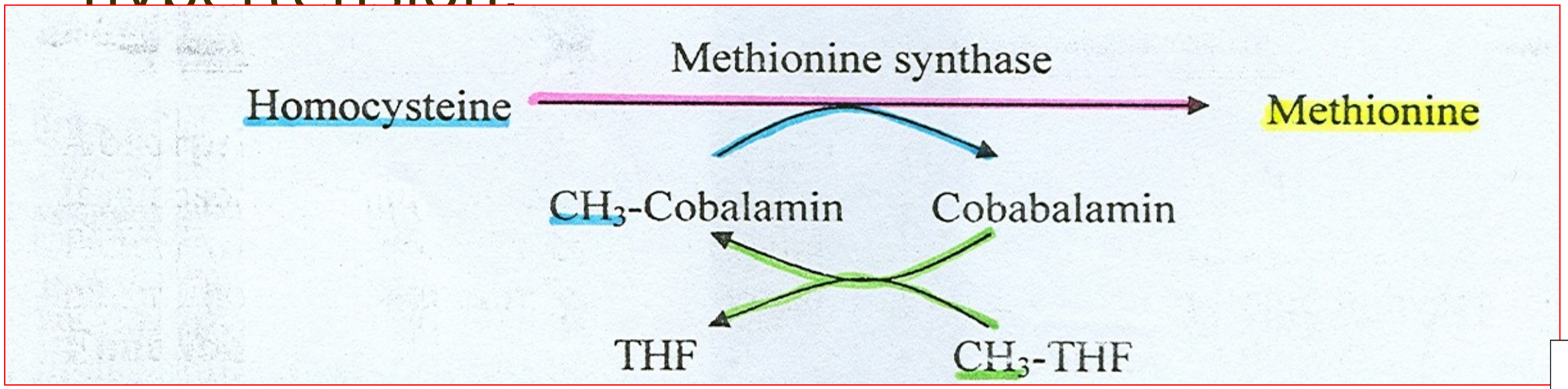
b)Methyl molonyl CoA

c)Succinyl CoA

d)Glycine

Explain the possible cause of hypertension although the patient is vegetarian

Elevated blood level of homocysteine is a significant risk factor for development of atherosclerosis, thrombosis and hypertension.

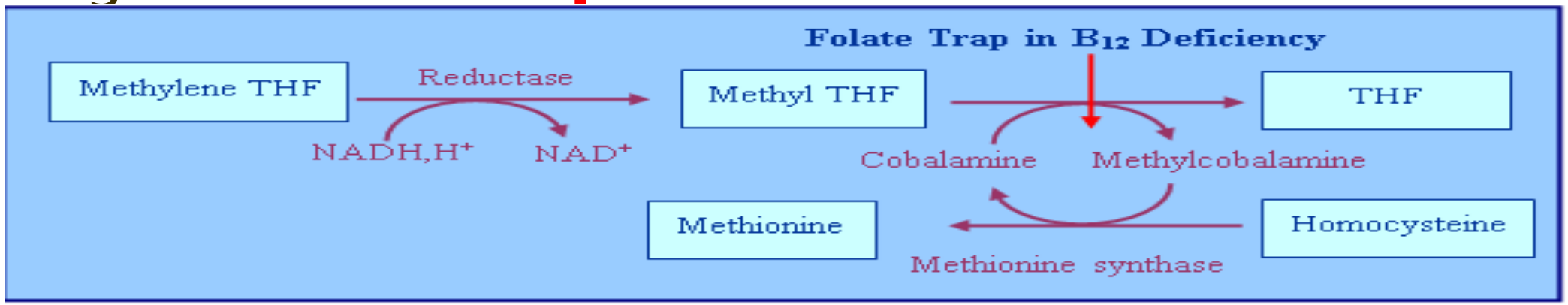


Discuss the mechanism of development of anemia in patients with vit B12 deficiency

Pernicious anemia:

Megaloblastic anemia due to functional folate deficiency (folate trap)

Vitamin B_{12} deficiency blocks the metabolism of folic acid and results in accumulation of methyl-THF leading to **folate trap**.



What is a possible cause of peripheral neuritis in this case?

Accumulation of methylmalonyl-CoA that will :

1. act as **competitive for malonyl-CoA** and produces inhibition of fatty acid biosynthesis required for synthesis of myelin sheath.

2. substitute malonyl-CoA in fatty acid synthesis leading to **production of branched-chain fatty acids** which disrupt membrane structure

Functions of TPP

Active form : thiamine pyrophosphate (TPP).

Functions of TPP: act as coenzymes for

1-Acts as coenzyme for oxidative decarboxylation of α-keto acids:

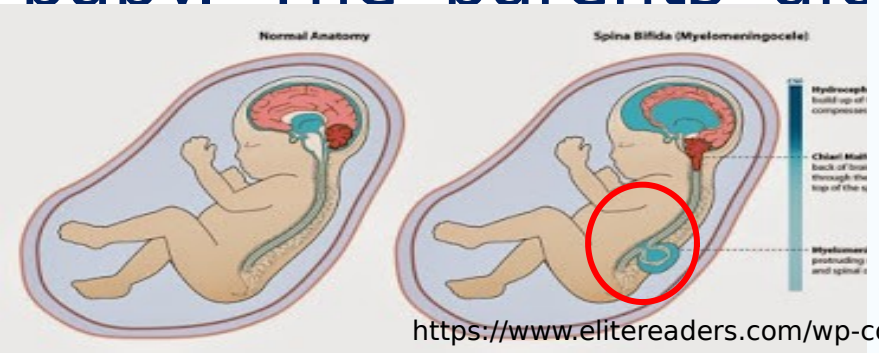
e.g.:

- **Pyruvate dehydrogenase complex (pyruvate to → acetyl-CoA)**
- **α-Ketogluterate dehydrogenase complex (α-KG to → succinyl-CoA)**
- **Branched chain α-Ketoacid dehydrogenase**

Case scenario

A30 years old woman pregnant for the third time at first trimester (no living child) with history of both pregnancies affected by neural tube defe[illegible] presented at 8 weeks period of g[illegible]ived (get pregnan[illegible]nd did not seek any antenatal care. [illegible]vered at a hospital and anencephaly was detected at birth. However, no comment was made on presence or absence of other anomalies. In the second pregnancy, gross congenital anomalies were detected in her baby. The parents dic[illegible]

What is the probable diagnosis?



https://www.elitereaders.com/wp-content/uploads/2018/04/anencephaly-ah-neath-baby-missing-skull-featured.jpg

Mention Causes of Folate deficiency

(1) Increase rate of cell division e.g. pregnancy, hemolytic anemia .

(2) Long term use of drugs:

oral contraception, estrogens, alcohol, and anticonvulsants (decrease absorption and increase catabolism of folate).

(3) Administration of methotrexate (inhibitor of dihydrofolate reductase) as anticancer chemotherapeutic.

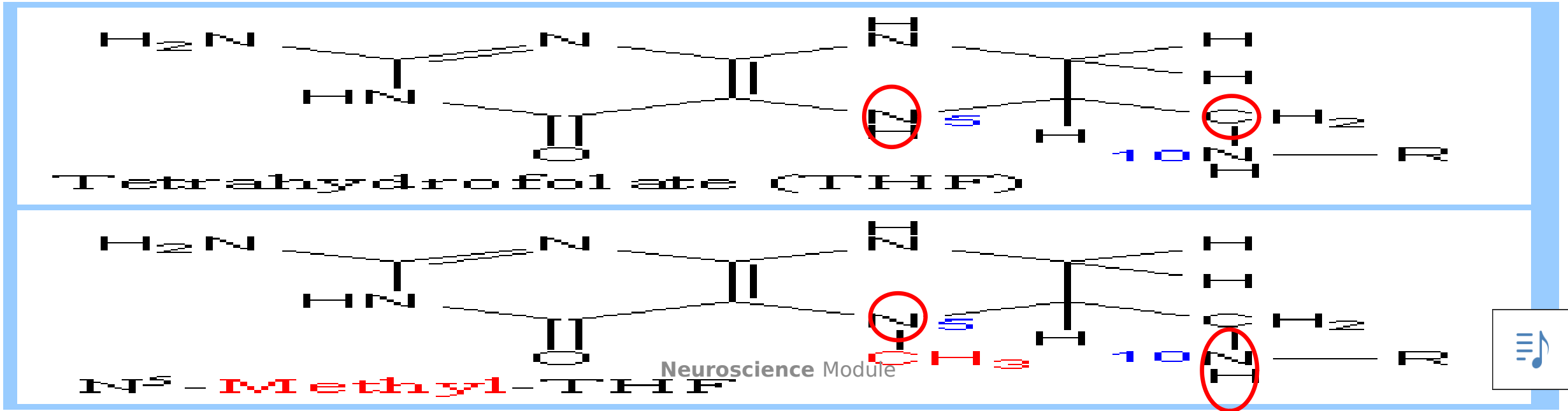
(4) Alcoholism

(5) Poor absorption: caused due to defect in the small intestine.

(6) Mycotoxins (type of fungus) in contaminated corn meal

Functions of THF

- **It acts as a carrier of one carbon groups which carried on** either to ***N^5 or N^{10} nitrogen atom or to both***
- **one carbon group is important for purine (it provides C2 and C8 of purine ring) and the synthesis of dTMP of pyrimdine (DNA synthesis) and methionine (which is required for methylation reaction through SAM (S-Adenosyl methionine) especially in rapidly dividing cells e.g. developing RBCs in bone marrow, surface epithelial cells of mouth, GIT, urinary tract, and respiratory tract** and also **growing fetus.**



Explain on a biochemical basis Megaloblastic anemia in folate deficiency?

folate deficiency → **Inadequate serum levels of folate**

↓

No one carbon unit carried → **No synthesis of purines and pyrimidines (TMP)**

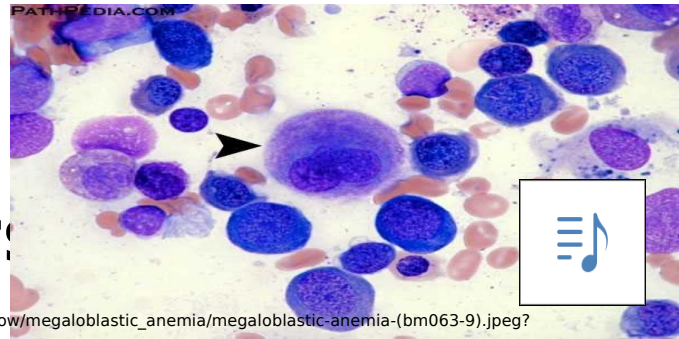
↓

Inhibition of DNA synthesis in rapidly dividing cells as bone marrow cells

↓

megaloblastic anemia

accumulation of megaloblast



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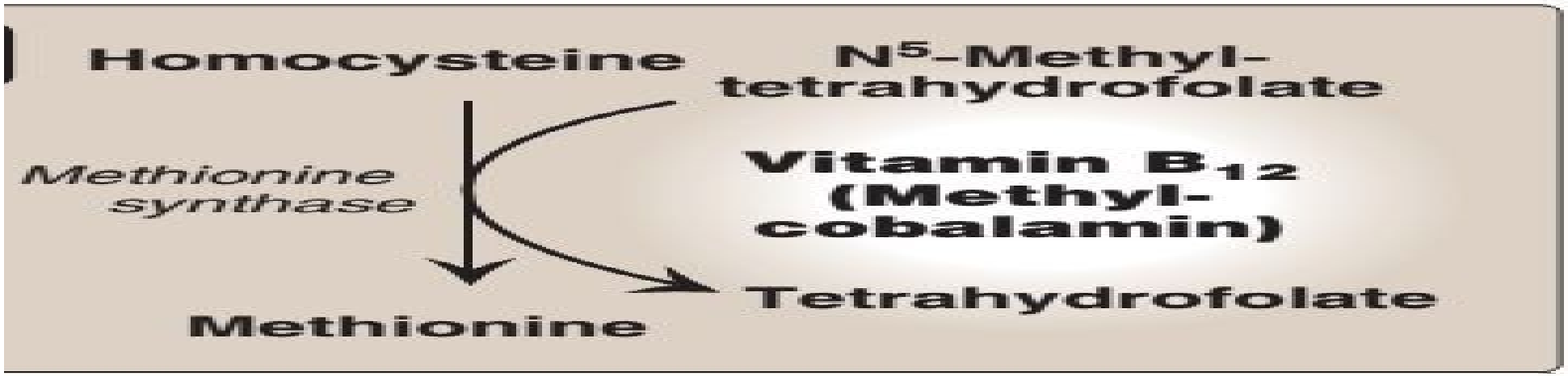
Explain on a biochemical causes NTD in folic acid deficiency?

Folate is required for the production and maintenance of new cells, for DNA synthesis and RNA synthesis because it is needed to carry one carbon groups for:

- Methionine which is needed for methylation reaction through SAM
- nucleic acid synthesis.

- The early human embryo may be particularly susceptible to folate deficiency due to high demand for post translational methylations of the cytoskeleton in neural cells during neural tube ~~closure~~ → during embryogenesis neural tube defects



Discuss Folate Analogues

1. Methotexate & aminopetrin

- They are potent inhibitors of human dihydrofolate reductase; so prevent folate activation to THF.
- As THF used in purines & thymine synthesis, folate analogues are applied therapeutically as blockers of tumor growth (anticancer drug or chemotherapy).
- .

2. Trimethoprim

-They are competitive inhibitor of bacterial dihydrofolate reductase.

-It inhibits DNA synthesis in bacteria.

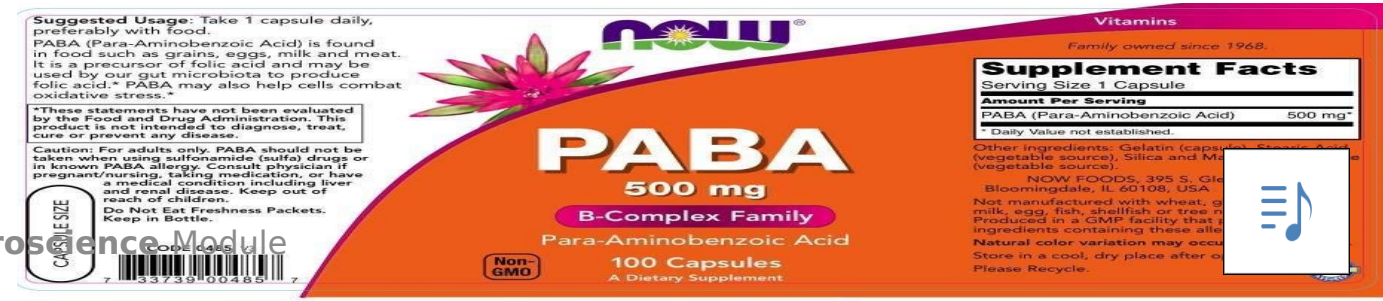
-It is applied as antibiotic.

3. Sulfonamide

-It is PABA (Para-aminobenzoic acid; part of folic acid) analogue

-It inhibits synthesis of folic acid only in bacteria

-Used as antibiotic.


Suggested Usage: Take 1 capsule daily, preferably with food.
PABA (Para-Aminobenzoic Acid) is found in food such as grains, eggs, milk and meat. It is a precursor of folic acid and may be used by our gut microbiota to produce folic acid.* PABA may also help cells combat oxidative stress.*
*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
Caution: For adults only. PABA should not be taken when using sulfonamide (sulfa) drugs or in known PABA allergy. Consult physician if pregnant/nursing, taking medication, or have a medical condition including liver and renal disease. Keep out of reach of children.
Do Not Eat Freshness Packets. Keep in Bottle.
CAPSULE SIZE
now
Vitamins
Family owned since 1968.
PABA
500 mg
B-Complex Family
Para-Aminobenzoic Acid
100 Capsules
A Dietary Supplement
Non-GMO
Supplement Facts
Serving Size 1 Capsule
Amount Per Serving
PABA (Para-Aminobenzoic Acid) 500 mg*
* Daily Value not established.
Other ingredients: Gelatin (capsule), Silica and Ma (vegetable source), Silica and Ma (vegetable source).
NOW FOODS, 395 S. Gle Bloomingdale, IL 60108, USA
Not manufactured with wheat, g milk, egg, fish, shellfish or tree n Produced in a GMP facility that p ingredients containing these alle
Natural color variation may occu
Store in a cool, dry place after o
Please Recycle.

Thank you